

### **REMARKS**

Reconsideration of the allowability of the present application is requested respectfully.

#### **Status of the Claims**

All of the pending claims, that is, claims 54 to 56, 58 to 92, and 94 to 113 have been acted upon by the Examiner. No claims have been allowed. Claims 54, 61, 76, 79, 82, 83, 86, 87, 90, and 111 have been amended. No claims have been canceled. Claims 114 and 115 have been added. Accordingly, claims 54 to 56, 58 to 92, and 94 to 115 are presented for examination.

Claims 54, 76, 79, 82, 83, 86, 87, 90, and 111 have been amended to remove the recitation "at pH 5.0 – 6.0". This recitation was added in the previous reply in order to distinguish the aforementioned claims from Fisher et al. (US 4,228,154). In addition to deleting this recitation from the claims, applicants hereby withdrawal all arguments related to this amendment.

Claim 61 has been amended to recite "(i) pH adjustment". Support for this amendment is found in Claim 61 as originally submitted in the amendment dated April 18, 2003.

In view of the amendments to Claims 54 and 90, new Claims 114 and 115, which depend from Claims 54 and 90, respectively, have been added to provide a specific pH range for cationic exchange to be performed. New Claims 114 and 115 are the same as previously canceled Claims 57 and 93, except Claim 114 has been amended to recite "the albumin solution that undergoes cation exchange chromatography" instead of "the initial albumin solution". Support for these claims is found on page 6, lines 15 to 17, of the application.

## **ARGUMENTS**

### **Summary of the Rejections**

#### **The 35 U.S.C. §103(a) Rejections**

The Examiner has presented a variety of §103(a) rejections, each of which is discussed in turn below. All of the §103(a) rejections are based entirely or in part on the combination of Goodey et al (WO 97/31947) and Fisher et al. (US 4,228,154). As discussed below, Goodey et al. discloses purification of albumin using techniques that require albumin binding to cationic or anionic resins while Fisher et al. states that such methods are to be avoided.

Goodey et al. discloses purification of albumin using positive mode, with respect to albumin, cationic exchange ("positive CE"). Page 17, lines 1 to 9, of Goodey et al. further indicates that this positive CE step must be done first. Accordingly, the methods of Goodey et al. require adsorption of albumin to a cation exchange resin followed by elution, or desorption, of the albumin from the cation ion exchange resin.

Fisher et al. is directed to a process of purification of albumin "in the absence of process steps involving precipitation or desorption of the albumin" (see abstract of Fisher et al.; emphasis added). Column 1, line 63, to Column 2, line 17, of Fisher et al. further states:

It is noteworthy, for example, that known ion exchange chromatographic methods for purification of albumin often involve multiple precipitation and resuspension steps similar to those extant in the cold alcohol fractionation processes and further involve multiple desorptions of the albumin from the ion exchanger materials. Each such manipulation increases the potential for adverse changes in the native character of the albumin molecules.

There exists, therefore, an ongoing need for new procedures which will efficiently isolate purified albumin from plasma while minimizing potential alterations in the native structure or character of

the albumin or other plasma components. A reduction in handling or manipulation, with or without greater yield has obvious advantages in commercial applications as well.

## BRIEF SUMMARY

According to the present invention, "chromatographically pure" plasma albumin is obtained in high yields by ion exchange chromatographic procedures which maintain the albumin in a solution phase throughout processing.

Maintenance of "albumin in a solution phase throughout processing" requires that the albumin never be bound to any resin. In other words, Fisher et al. requires that the albumin not enter the "solid-phase". Accordingly, Fisher et al. discloses purification of albumin using methods which do not require adsorption to either anion or cation resins. Example 1 of Fisher et al. discloses negative mode anionic exchange ("negative AE") followed by negative mode cationic exchange ("negative CE"). As all of the purification steps of Fisher et al. are "negative", use of the method of Fisher et al. ensures that albumin will never bind to a resin and be later eluted or desorbed from the resin. Thus, the methods of Fisher et al. do not require adsorption and desorption of albumin from either cationic or anionic resins. Furthermore, Fisher et al. requires that no desorption occur. Indeed the absence of desorption is the goal of Fisher et al.

### The 35 U.S.C §103(a) Rejections

#### A. The 35 U.S.C. §103(a) Rejections of Claims 54, 56, 59 to 67, 69, 70, 71, 74 to 76, 78, 79, 81, 90, 92, 95 to 102, 104 to 106, and 109 to 111

The Examiner has rejected Claims 54, 56, 59 to 67, 69, 70, 71, 74 to 76, 78, 79, 81, 90, 92, 95 to 102, 104 to 106, and 109 to 111 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al.

Applicants respectfully traverse the rejections.

Applicants submit that the Examiner has not satisfied all of the three basic criteria required to establish a *prima facie* case of obviousness. MPEP §2143 states:

“To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the publications themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or publications when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaack*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).”

In the arguments presented below, applicants will demonstrate that there is no motivation to modify or combine Goodey et al. and Fisher et al.

Goodey et al. discloses positive CE. Fisher et al. discloses negative CE and negative AE with the goal that desorption of albumin is to be avoided. There is no evidence of record that would suggest to or motivate one skilled in the art that the disclosures of these publications be combined; in fact, the disclosure of Fisher et al. suggests that they not be combined.

The abstract of Fisher et al. states, “Purified plasma albumin is obtained by ion exchange chromatographic procedures and in the absence of process steps involving precipitation or desorption of the albumin”. Column 2, lines 36 to 38, of Fisher et al. state: “At no point in the process of the invention is the albumin precipitated or removed from the solution phase”. Accordingly, the methods of Fisher et al. specifically require that the albumin must not bind to any solid resin as such binding would result in removal of the albumin from the solution phase and require desorption to re-enter the solution phase.

In stark contrast, Goodey et al. discloses positive CE, which requires binding to a solid resin followed by desorption. Accordingly, the teachings of Goodey et al. are in direct conflict with Fisher et al. MPEP §2143.01 states:

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants submit that to use the invention of Fisher et al. in conjunction with Goodey et al. would constitute a modification of Fisher et al. which is unsatisfactory for its intended purpose. Accordingly, the Examiner's combination of Goodey et al. and Fisher et al. is invalid because the criteria that a suggestion or motivation to modify the teachings of the publications or to combine the publication teachings has not been met.

MPEP §2141 states (emphasis added), "The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination". In considering Fisher et al. in its entirety, it is clear that Fisher et al. not only directly conflicts with Goodey et al., it teaches away from Goodey et al. and the claimed invention. Applicants respectfully submit that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the publications must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of skill in the art would, upon reviewing Goodey et al. and Fisher et al., have selectively ignored those portions of Fisher et al. that are in conflict with Goodey et al. Without the present application, one of ordinary skill in the art would have no basis to selectively ignore those conflicting portions of Fisher et al.

In view of the above, applicants respectfully request that the rejection Claims 54, 56, 59 to 67, 69, 70, 71, 74 to 76, 78, 79, 81, 90, 92, 95 to 102, 104 to 106,

and 109 to 111 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. be withdrawn.

**B. The 35 U.S.C. §103(a) Rejections of Claims 55, 77, 80, 82, 84, 86, 88, 91, and 112**

The Examiner has rejected Claims 55, 77, 80, 82, 84, 86, 88, 91, and 112 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Shaklai et al.

Applicants respectfully traverse the rejections.

Shaklai et al. has been applied for the teaching that glycosylated albumin peptides can bind to cation exchange resins. This teaching provides no motivation to combine Goodey et al. and Fisher et al. as noted above. Since Shaklai et al. does not provide any information that overcomes the deficient *prima facie* case of obviousness, applicants respectfully request withdrawal of the obviousness rejection of Claims 55, 77, 80, 82, 84, 86, 88, 91, and 112, which additionally relies on Shaklai et al.

**C. The 35 U.S.C. §103(a) Rejections of Claims 58 and 94**

The Examiner has rejected Claims 58 and 94 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Curling (Methods of Plasma Fractionation, PP.77-91 (1980)).

Applicants respectfully traverse the rejections.

Curling has been applied for the teaching industrial scale purification of albumin on AE and CE columns, with 500 g of albumin in 16 L (approximately 31 g/L). This teaching provides no motivation to combine Goodey et al. and Fisher et al. as noted above. Since Curling does not provide any information that overcomes the deficient *prima facie* case of obviousness, applicants respectfully request

withdrawal of the obviousness rejection of Claims 58 and 94, which additionally relies on Curling.

In addition, Curling discloses positive AE and positive CE with respect to albumin (pages 80 to 81, including Figure 2). As discussed above, Fisher et al. teaches away from chromatographic methods that require binding of albumin to the solid-phase. Accordingly, one skilled in the art would not be motivated to combine Fisher et al. with Curling.

In view of the above, applicants respectfully request that the rejection Claims 58 and 94 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al. in view of Fisher et al., and further in view of Curling be withdrawn.

**D. The 35 U.S.C. §103(a) Rejections of Claims 68, 73, 103, and 108**

The Examiner has rejected Claims 68, 73, 103, and 108 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Ohmura et al. (EP0570916) and Chang (EP0422769).

Applicants respectfully traverse the rejections.

Ohmura et al. has been applied for the teaching that albumin can be adsorbed onto an AE column at a pH of 6 to 8, and eluted from the column using buffer with the same pH, but higher salt concentrations. Chang has been applied for the teaching that albumin becomes readily bound to AE columns at a pH greater than 6.1. These teachings provide no motivation to combine Goodey et al. and Fisher et al. as noted above. Since Ohmura et al. and Chang do not provide any information that overcomes the deficient *prima facie* case of obviousness, applicants respectfully request withdrawal of the obviousness rejection of Claims 68, 73, 103, and 108, which additionally rely on Ohmura et al. and Chang.

In addition, Ohmura et al. (page 5, lines 34 to 44, and page 6, lines 8 to 21) discloses positive AE with respect to albumin. As discussed above, Fisher et al.

teaches away from chromatographic methods that require binding of albumin to the solid-phase. Accordingly, one skilled in the art would not be motivated to combine Fisher et al. with Ohmura et al.

Furthermore, like Fisher et al., Chang teaches away from using positive ion exchange chromatography to purify albumin. Page 3, lines 16 to 21, of Chang states:

Although ion-exchange chromatography has previously been used to purify albumin, the known methods are undesirably expensive and inefficient. For example, in one method, the albumin (instead of contaminating proteins) is bound to the ion-exchange resin. This method requires the use of large amounts of resin to bind large amounts of albumin present in the impure albumin solution. This results in undesirably-high resin costs and long reaction times.

A more efficient and economical method of purifying albumin by ion-exchange chromatography, is to bind the contaminants, which are present in the impure albumin solutions in much smaller amounts than albumin, to the resin.

Accordingly, Chang also teaches away from using positive AE or CE to purify albumin. Thus, like Fisher et al., one skilled in the art would not be motivated to combine Goodey et al. with Chang.

The Examiner has stated that the motivation to combine Goodey et al. and Fisher et al. with Ohmura et al. is found page 4, lines 31 to 33, of Chang, which states:

At a pH of more than about 6.1, the albumin, rather than the contaminating proteins, becomes more readily bound to the resin, and less than the desired amount of impurities precipitate.

Taken with the passage from Page 3, lines 16 to 21, of Chang, it is clear that Chang teaches that having the albumin bind to the column at a pH greater than 6.1 is to be avoided, and thus does not provide a motivation to perform positive AE with respect to albumin at pH 6.0 – 8.0. Accordingly, applicants submit that not only



does Chang does not provide a motivation to combine Ohmura et al with Goodey et al., and Fisher et al., but actually discourages such a combination.

Applicants submit that to use the invention of Goodey et al. and Ohmura et al. in conjunction with Chang would constitute a modification of Chang which is unsatisfactory for its intended purpose. Accordingly, the Examiner's combination of Goodey et al. and Ohmura et al. with Chang is invalid because the criteria that a suggestion or motivation to modify the teachings of the publications or to combine the publication teachings has not been met.

MPEP §2141 states (emphasis added), "The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination". In considering Chang in its entirety, it is clear that Chang not only directly conflicts with Goodey et al. and Ohmura et al., but also teaches away from Goodey et al., Ohmura et al., and the claimed invention. Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the publications must be considered as a whole. The Examiner has presented no objective evidence that one of skill in the art would, upon reviewing Goodey et al., Ohmura et al., and Chang, would have selectively ignored those portions of Chang that are in conflict with Goodey et al. and Ohmura et al. In particular, without the present application, one of ordinary skill in the art would have no basis to selectively ignore those conflicting portions of Chang.

In view of the above, applicants respectfully request that the rejection Claims 68, 73, 103, and 108 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Ohmura et al. and Chang be withdrawn.

**E. The 35 U.S.C. §103(a) Rejections of Claims 72 and 107**

The Examiner has rejected Claims 72 and 107 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Ohmura et al. and Chang.

Applicants respectfully traverse the rejections.

Ohmura et al. has been applied for the teaching that albumin can be adsorbed onto an AE column at a pH of 6 to 8 with a salt concentration of 0.001-0.05M, and eluted from the column using buffer with the same pH, but salt concentrations of 0.05 to 1M. Chang has been applied for the teaching that albumin becomes readily bound to AE columns at a pH greater than 6.1. These teachings provide no motivation to combine Goodey et al. and Fisher et al. as noted above. Since Ohmura et al. and Chang do not provide any information that overcomes the deficient *prima facie* case of obviousness, applicants respectfully request withdrawal of the obviousness rejection of Claims 72 and 107, which additionally rely on Ohmura et al. and Chang.

In addition, for reasons noted above, one skilled in the art would not be motivated to combine Fisher et al. with Ohmura et al. Also, one skilled in the art would not be motivated to combine Goodey et al. or Ohmura et al. with Chang.

In view of the above, applicants respectfully request that the rejection Claims 72 and 107 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and further in view of Ohmura et al. and Chang be withdrawn.

**F. The 35 U.S.C. §103(a) Rejections of Claims 83, 85, 87, and 89**

The Examiner has rejected Claims 83, 85, 87, and 89 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and Shaklai et al. and further in view of Chang.

Applicants respectfully traverse the rejections.

Chang has been applied for teaching that AE chromatography steps to remove contaminating proteins from albumin solution can be repeated. This teaching provides no motivation to combine Goodey et al. and Fisher et al. as noted above. Since Chang does not provide any information that overcomes the deficient *prima facie* case of obviousness, applicants respectfully request withdrawal of the obviousness rejection of Claims 83, 85, 87, and 89, which additionally rely on Chang.

In addition, for reasons noted above, one skilled in the art would not be motivated to combine Goodey et al. with Chang.

Furthermore, Chang teaches repeating *negative* AE steps, not *positive* AE steps as are required by Claims 83, 85, 87, and 89. Accordingly, the combination of Goodey et al., Fisher et al., Shaklai et al., and Chang do not recite all of the elements of Claims 83, 85, 87, and 89, which require repeating positive AE steps.

In view of the above, applicants respectfully request that the rejection of Claims 83, 85, 87, and 89 under 35 U.S.C. §103(a) as being unpatentable over Goodey et al., in view of Fisher et al. and Shaklai et al., further in view of Chang be withdrawn.

**G. The 35 U.S.C. §112, second paragraph, Rejections**

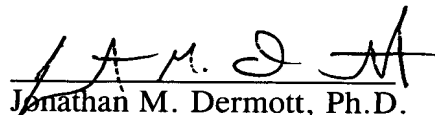
The Examiner has rejected Claims 82 and 84 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and claim the invention.

In re Application of Van Urk et al.  
Application No. 09/890,297  
Art Unit No. 1637

Atty Docket No. P27,692 USA  
September 10, 2004  
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Applicants have amended Claim 82 to recite "(xii) collecting the albumin-containing anion exchange flow through from step (xi);". In view of this amendment, applicants respectfully request that the rejection of Claim 82, and Claim 84 which depends from Claim 82, under 35 U.S.C. §112, second paragraph, be withdrawn.

Respectfully submitted,

  
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